REMARKS

Applicant wishes to thank Examiner Epps-Ford for the time and courtesy extended in the telephonic interview conducted on September 26, 2006 to discuss the allowability of certain currently presented claims. In the current amendment, claims 2-7, 11, 14, 21-27, 31, 32 and 37-39 are canceled. Claims 15-19 remain withdrawn. As such, claims 1, 8-10, 12, 13, 20, 28-30 and 33-36 are presented for examination.

Claims 1 and 12 are amended. Support for the claim amendments can be found throughout the specification and claims as filed. Accordingly, no new matter has been added by way of these amendments.

Reconsideration of the pending claims in view of the amendments and comments presented herein is respectfully requested.

Rejection of Claims 1, 4, 5, 8-13, 20, 28, 29-34 and 36-38 Under 35 U.S.C. §102

The Examiner rejects claims 1, 4, 5, 8-13, 20, 28-34 and 36-38 under 35 U.S.C. §102(a)/102(e) as being anticipated by U.S. Patent No. 6,172,216 (Bennett et al.), or alternatively, under 35 U.S.C. § 102(b) by WO 00/99504 (Baker et al.). In particular, the Examiner alleges that Bennett et al. disclose a 20 nucleobase oligomer having 9 contiguous nucleobases complementary to nucleobases 3258-3268 of SEQ ID NO: 3. Additionally, the Examiner asserts that Baker et al. disclose an 18 nucleobase oligomer that is 88.9% complementary to nucleotides 177 through 194 of SEQ ID NO: 3.

Applicants maintain that claims 1, 4, 5, 8-13, 20, 28-34 and 36-38 are novel in view of both Bennett et al. and Baker et al. However, in order to rapidly move this application to issuance, Applicants have canceled independent claim 11 and have amended independent claim 1 to recite "a non -catalytic oligonucleotide compound 20 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein B, wherein said compound (1) is fully complementary to the nucleotide sequence set forth in SEQ ID NO: 3 . . . . " Neither Bennett nor Baker teach a 20 nucleobase oligonucleotide compound that is fully complementary to the nucleotide sequence set forth in SEQ ID NO: 3.

In view of the foregoing remarks and amendment, Applicants respectfully request that the Examiner withdrawn the rejection of claims 1, 8-10, 12, 13, 20, 28-30, 33, 34 and 36 under 35 U.S.C. § 102.

Rejection of Claims 1, 4, 5, 8-13, 20, 28, 29-34 and 36-38 Under 35 U.S.C. §103(a)

The Examiner rejects claims 1, 4, 5, 8-13, 20, 28-39 under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 6,172,216 (Bennett et al.) in view of U.S. Patent Application Publication No. 2002/0068708 (Wengel et al.). In particular, the Examiner acknowledges that Bennett et al. does not disclose locked nucleic acid bicyclic sugar modifications but alleges that Wengel et al. provides this missing element. The Examiner further asserts that a skilled artisan would be motivated to combine the teachings Bennett et al. with those of Wengel et al. in order to produce antisense oligonucleotides having, among other alleged properties, increased stability.

Applicants maintain that each of claims 1, 4, 5, 8-13, 20, 28-39 is patentable over the combination of Bennett et al. and Wengel et al., however, to expedite the issuance of the instant application, Applicants have canceled independent claim 11 and have amended independent claim 1 as described above. Because the combination of Bennett et al. and Wengel et al. does not disclose a 20 nucleobase oligonucleotide compound that is fully complementary to the nucleotide sequence set forth in SEQ ID NO: 3, this combination of references does not render any of claims 1, 4, 5, 8-13, 20, 28-39 obvious.

In addition to the foregoing, the Examiner rejects claims 1, 4, 5, 8-13, 20 and 28-39 under 35 U.S.C. §103(a) as being obvious over WO 99/35241 (Rouy et al.) and Eggerman et al. (IDS 04-06-05) in view of GeneBank Accession No. NM_000384, U.S. Patent No. 5,656,612 (Monia et al.), Agrawal et al. and Wengel et al. In particular, the Examiner asserts that together Rouy et al. and Eggerman et al. demonstrate that "antisense oligonucleotides targeted for apoB decreased apoB mRNA expression in human liver cell lines by up to 80%." The Examiner acknowledges that this combination does not disclose modified non-catalytic compounds of 12 to 30 nucleobases in length than hybridize to a region excluding the start codon region and which inhibit apolipoprotein B mRNA levels when applied *in vitro* at a concentration of 150 nM to HepG2 cells. The Examiner, however, alleges that this deficiency is made up by the GenBank reference disclosing the full-length apolipoprotein B mRNA in combination with the Monia et al.

reference, which allegedly discloses chimeric oligonucleotide and modified oligonucleotides, and the Agrawal et al. reference, which allegedly discloses that it is preferable to screen numerous antisense oligonucleotides to identify optimal target sites. Finally, the Examiner cites Wengel et al. as disclosing locked nucleic acid bicyclic sugar modifications. The Examiner alleges that a skilled artisan would be motivated to combine this assortment of references in order to develop a collection of stabilized oligonucleotides to various regions of the gene that would permit one "to further elucidate the role of that gene of interest in various cellular processes."

Applicants respectfully disagree with the Examiner's position that claims 1, 4, 5, 8-10, 12, 13, 20, 28-30, and 33-36 are obvious over the combination of Rouy et al., Eggerman et al. (IDS 04-06-05), GeneBank Accession No. NM_000384, Monia et al., Agrawal et al. and Wengel et al. This combination of references amounts to no more than an invitation to screen antisense oligonucleotides along the length of the apolipoprotein B mRNA. The Examiner has simply taken a reference specific to the apolipoprotein B mRNA sequence (GenBank Accession No. NM_000384) and has combined it with references that hint at making antisense nucleic acids targeted to a nucleic acid encoding apolipoprotein B (Rouy et al. and Eggerman et al.). These references have been further combined with general antisense references that are routinely applied to every modified antisense nucleic acid (Monia et al., Agrawal et al. and Wengel et al.).

Although GenBank Accession No. NM_000384 does disclose a nucleic acid encoding apolipoprotein B, neither Rouy et al. nor Eggerman et al. disclose any oligonucleotides to the mRNA encoding apolipoprotein B. At best Rouy et al. invite the skilled artisan to make antisense oligonucleotides to a nucleic acid encoding apolipoprotein B. Eggerman et al. states that apolipoprotein B mRNA production may be inhibited up to 80% but does not disclose any representative oligonucleotides or concentrations at which the oligonucleotide is effective. In contrast, Applicants have discovered several oligonucleotides that can target a nucleic acid encoding apolipoprotein B and can produce extensive inhibition (70% or greater inhibition) of apolipoprotein B mRNA at extremely low concentrations (concentrations of 150 nM). The cited references do not teach a skilled artisan even one specific oligonucleotide that would inhibit the production of apolipoprotein B to the extent recited in claim 1. Furthermore, these references do not even suggest that one could find an oligonucleotide that would produce such effective inhibition at such low concentrations. Even if a skilled artisans were motivated to combine the

teachings of the multitude of references cited above, they would arrive at nothing more than an invitation to try to develop one or more oligonucleotides to inhibit apolipoprotein B. "Obvious to try" is not the legal test for obviousness in the United States. See *Hybridtech, Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367 (Fed. Cir. 1986) and *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.,* 806 F.2d 1565 (Fed. Cir. 1986). Quite simply, the cited references do not show a even a single oligonucleotide compound targeted to a nucleic acid encoding apolipoprotein B that can produce at least 70% inhibition of apolipoprotein B mRNA at a concentration of 150 nM. Furthermore, the skilled artisan would have no reasonable expectation that s/he would ever find even one oligonucleotide that could produce such high level inhibition at such low oligonucleotide concentrations.

In view of the foregoing remarks and amendment, Applicants respectfully request that the Examiner withdraw the rejection of claims 1, 8-10, 12, 13, 20, 28-30 and 33-36 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants believe that all outstanding issues in this case have been resolved and that the present claims are in condition for allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is invited to contact the undersigned at the telephone number provided below in order to expedite the resolution of such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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